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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/689,430	10/12/2000	Christopher E. Walsh	35052/204373 (5052-53)	7095

826 7590 09/11/2002

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EXAMINER
LI, QIAN J

ART UNIT	PAPER NUMBER
1632	13

DATE MAILED: 09/11/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/689,430	Applicant(s)	
	Examiner Janice Li	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20 and 58-90* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20 and 58-90* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

The Declaration under 37 CFR 1.131 and amendment filed on June 24, 2002 have been entered and assigned as Papers #11 and 12. Claims 21-57 have been canceled. Claim 18 has been amended. Claims 68-90 are newly submitted. Claims 1-20 and 58-90 are pending and under current examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18, 19 and 35 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, and the rejection applies to the newly submitted claims 68-90.

These claims are directed to a rAAV comprising a heterologous sequence encoding a B-domain deleted factor VIII selected from the group consisting of a sequence that hybridizes to nucleotides 419-4835 of the SEQ ID No: 1 under conditions of high stringency, the amended claims add a functional phrase, "which encodes a biologically active B-domain deleted factor VIII". The newly submitted claims

encompass sequences that are at least 75-95% identical to nucleotides 419-4835 of SEQ ID No: 1 and encodes a biologically active B-domain deleted factor VIII.

In response to the lack of written description rejection, applicants argue in paper #12, that applicant have provided representative species of B-domain deleted factor VIII sequences in lines 24-30 of page 20 of the specification; that these claims recite nucleotide sequences that hybridize to recited nucleotides 419-4835 of the SEQ ID No: 1 under conditions of high stringency, and the nucleotide sequence that art at least 75-95% identical to nucleotides 419-4835 of the SEQ ID No: 1; that the functional characteristics are further provided.

The arguments have been carefully considered but found not persuasive for reasons of record set forth in Paper #8 and following.

As indicated in Paper # 8 and reiterated here, polynucleotide sequences limited by hybridization conditions, even under relatively high stringent conditions, encompass large amount sub-sequences that are unknown and unsequenced, which may not encode a functional Factor VIII or which may generate an amino acid sequence that is irrelevant to the recited Factor VIII. For example, the specification lists different hybridization and washing conditions (paragraph bridging pages 23-24), but fails to teach which of these conditions would yield a sequence that is 75% or 95% identical sequence with nucleotides 419-4835 of the SEQ ID No: 1, and out of numerous sequences hybridized, which of these sequences would have a proper function of B-domain deleted factor VIII. The specification cites *///* reference (line 28 of page 20), in which the B-domain deleted factor VIII share 99.8% homology with 419-4835 of the

SEQ ID No: 1. Even thought there are functional variants of B-domain deleted Factor VIII that do fall into the range of the claims, the claims embrace large amount of other sequences non-described, and there is no known or disclosed correlation between the function of B-domain deleted factor VIII and the structure of non-described nucleic acids that are 75-95% identical to 419-4835 of the SEQ ID No: 1.

The state of the art in protein chemistry is probably one of the most unpredictable areas of biotechnology. Considering the possible numbers of polypeptide variants, the art known knowledge is "EACH POSITION IN A PEPTIDE IS UNIQUELY DEFINED, THE NUMBER OF POSSIBLE PEPTIDES IS VERY LARGE, EVEN IN A RELATIVELY SHORT PEPTIDE. WHEN THE NUMBER OF AMINO ACID UNITS IN THE PEPTIDE CHAIN EQUALS *N*, THE NUMBER OF POSSIBLE PEPTIDES IS 20^N. THE PREPARATION OF A SPECIFIC PEPTIDE SEQUENCE AND THE DETERMINATION OF THE SEQUENCE OF AMINO ACIDS IN A PEPTIDE OR PROTEIN CHAIN REQUIRES SPECIFICALLY ADAPTED CHEMICAL METHODS." (*Encyclopedia Britannica online*). Although the polynucleotide coding region determines amino acid sequence of the protein, it is the ability of three-dimensional structures that allows the protein to function and carry out the messages of the genome. *Bowie et al* (Science 1990 Mar; 247:1306-10) teach that certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or none at all (page 1306, column 2). It is highly unpredictable, based on sequence homology alone, that sequence homologues will have the same activity as that protein to which they are being compared. This is because one cannot accurately predict the effects of the dissimilarities in the sequences identified by 419-4835 of the SEQ ID No: 1. *Everett et al* (Nat Genetics 1997;17:411-22) use sophisticated computational modeling based on

sequence homology to determine that the gene product causing Pendred syndrome was a sulphate transporter. However, subsequent research and investigation into the actual functional properties of the protein revealed that the protein was actually a chloride-iodide transporter and not a sulphate transporter as was originally predicted based on sequence homology (*Scott et al,* Nat Genetics 1999 Apr;21:440-443). *Bork* (Genome Res 2000:10;398-400) teaches the power and pitfalls associated with comparative sequence analysis for predicting protein function, and points out that based on the observation interacting proteins in one organism sometimes have homologs in other organisms, *Marotte et al* predicted novel interactions for 50% of yeast proteins using gene fusion information. However, they noted an overlap with classical methods and an error rate of 82% (left column in page 400). Therefore homology alone is not sufficient to describe the genus of the claimed nucleic acids, and accordingly does not provide a reasonable guide for those seeking to practice the invention. Weighing all factors in view of the level of knowledge and skill in the art, one skilled in the art would not recognize from the disclosure that the applicant was in possession of the genus of promoters comprising 75-95% sequence homology with or hybridize to 419-4835 of the SEQ ID No: 1.

For reasons of record and set forth in the preceding paragraphs, the specification fails to meet the written description provision of 35 U.S.C. §112, first paragraph.

Claims 18, 19, and 35 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making and using a rAAV vector

comprising a heterologous nucleotide sequence encoding a B-domain deleted factor VIII, wherein the said sequence is selected from the group consisting of a sequence given as nucleotides 419-4835 of the SEQ ID No: 1 or differs from nucleotides 419-4835 of the SEQ ID No: 1 due to the degeneracy of the genetic code, does not reasonably provide enablement for making and using a rAAV vector comprising a heterologous nucleotide sequence encoding a B-domain deleted factor VIII, wherein the said sequence is selected from the group consisting of a sequence that *is 75-95% identical* to or *hybridizes* under conditions of high stringency with nucleotides 419-4835 of the SEQ ID No: 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

In paper # 12, applicants argue that the specification provides the method for mutations and assay methods for identification of function B-domain deleted factor VIII variants. Thus, the skilled artisan could choose among possible modifications to produce polypeptides within the structural parameters set forth in the claims and test these modified variants to determine if they have the requisite biological activity of factor VIII. Although some quantity of experiment is required, the level of experimentation is not undue.

The arguments have been carefully considered but found not persuasive for reasons of record advanced in Paper #8 and the following.

The claims are not limited to a few possible modifications but encompass a large amount of sequences which are unsequenced and untested, even thought the assay

methods are known in the art, testing for these large amount of sequences requires painstaking experimentation. *Rudinger* (Peptide Hormones 1976; June;pages 1-7) teaches the relationship of sequence components and the peptide hormone function "THE SIGNIFICANCE OF PARTICULAR AMINO ACIDS AND SEQUENCES FOR DIFFERENT ASPECTS OF BIOLOGICAL ACTIVITY CANNOT BE PREDICTED *A PRIORI* BUT MUST BE DETERMINED FROM CASE TO CASE BY PAINSTAKING EXPERIMENTAL STUDY." (last paragraph of text on page 6).

Therefore, according to the current levels of the skill, determination of the effects of particular sequence changes is not predictable until they are actually made and used, hence resulting in a trial and error situation. Therefore, the general knowledge and levels of skill in the art do not supplement the omitted guidance, because specific, not general guidance is what is needed. fails to provide a reasonable guide for those seeking to practice the invention. Therefore, in view of the limited guidance, the lack of predictability of the art and the breadth of the claims, it would have required undue experimentation by the skilled artisan to practice the invention as it is broadly claimed.

For reasons of record and set forth in the preceding paragraphs, the specification fails to meet the enablement provision of 35 U.S.C. §112, first paragraph.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The prior rejection of claims 1, 3-18, 20-63, 65, and 67 under 35 U.S.C. 102(e) as being anticipated by *Couto et al* (US 6,221,349), and as evidenced by *Ill et al* (US 5,744,326) is withdrawn in view of the Declaration under 37 CFR 1.131.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The prior rejection of claims 1-63, 65, and 67 under 35 U.S.C. 103(a) as being unpatentable over *Couto et al* (US 6,221,349) as applied to claims 1, 3-18, 20-63, 65, and 67 above, and further in view of *GAO et al* (US 6,258,595) is withdrawn in view of the Declaration under 37 CFR 1.131.

Claims 1, 3-18, 20, 58-90 are rejected under 35 U.S.C. 103(a) as unpatentable over *Dwarki et al* (US 6,221,349), in view of *Robbins* (Pharmacol Ther 1998;80:35-47) and *Pittman et al* (Blood 1993;81:2925-35), and evidenced by *Vorachek et al* (J Bio Chem 2000 Sep;29031-41).

These claims are directed to a recombinant adeno-associated vector (rAAV) comprising a heterologous nucleotide sequence encoding B-domain deleted factor VIII operably linked with at least one enhancer and promoter, wherein said B-domain

deleted factor VIII comprising the amino acid sequence set forth in SEQ ID No: 2; wherein the rAAV is selected from the group consisting of serotypes 1-5 of AAV; wherein the factor VIII is operably linked with a liver-preferred expression control element, such as the hepatitis B virus EnhI enhancer comprising the sequence given as about nucleotide 419-4835 of the SEQ ID No: 1, and further comprising at least one transcription factor binding site, such as ATF box; wherein the promoter is an AAV ITR; wherein the rAAV vector is in a pharmaceutically acceptable carrier; wherein the liver specific promoter is the mouse albumin promoter; wherein the heterologous sequence further comprises a polyadenylation sequence comprising the sequence given as about nucleotides 150-4914 of the SEQ ID No: 1; wherein the heterologous nucleotide sequence of the rAAV is selected from the group consisting of a nucleotide sequence that hybridizes under high stringency condition to 419-4835 of the SEQ ID No: 1.

Dwarki et al teach a rAAV selected from anyone of the AAV serotype 1-7 and comprising an AAV ITR (column 5, lines 3-4), wherein the vector could encode a factor VIII (column 9, line 44) operably linked to an AFP enhancer and albumin promoter (column 6, line 35), which is a liver-preferred expression control element and has a HNF1 binding site as evidenced by Vorachek et al; the vector further comprising polyadenylation sequence (column 10, line 11). *Dwarki et al* also teach a method of producing rAAV stock and at 120 hrs, the total viral particles reached about 10^{12}. ($9x10^{11}$, table 1). The full length Factor III sequence comprises or at least 75% identical to 150-4835 of the SEQ ID No: 1, and comprises the HBV EnhI enhancer as indicated in claim 12. *Dwarki et al* do not teach a plasmid pDLZ6, but other plasmid vectors such as

pJM17. *Dwarki et al* do not teach B domain deleted factor VIII, but implicitly teach the size limitation for AAV vectors (column 7, lines 43-55).

Robbins et al teach various art-known viral vectors for gene therapy, that current methods of AAV preparation can result in stocks of up to 10^{14} particles/mL, and that AAV is an excellent gene transfer vehicle for delivery of genes smaller than 5kb (page 40).

Pittman et al teach that B-domain deleted factor VIII do not contain significant new antigenic epitope, tolerated well on infusion into FVIII-deficient dogs and was able to correct the cuticle bleeding time similar to wild-type recombinant factor VIII. They concluded that B-domain-deleted FVIII might be efficacious in treatment of hemophilia A in humans (abstract).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the vector taught by *Dwarki et al* using a vector of choice and simply substituting the full length factor VIII with a B-domain-deleted FVIII comprising a coding region of less than 5kb as taught by *Pittman et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed vector because rAAV is well-suited for gene delivery but requires a smaller insertion size of heterologous sequences as taught by *Robbins et al*. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 1-20, and 58-90 are rejected under 35 U.S.C. 103(a) as unpatentable over *Dwarki et al* (US 6,221,349), *Robbins* (Pharmacol Ther 1998;80:35-47) and *Pittman et al* (Blood 1993;81:2925-35) as applied to claims 1, 3-18, 20, 58-90 above, and further in view of *Gao et al* (US 6,258,595).

Claims 2 and 19 are further directed to a DNA spacer in the rAAV construct, the combined teachings of *Dwarki et al*, *Robbins,* and *Pittman et al* fail to teach such a spacer. However, before the instant application was filed, *Gao et al* teach to include a DNA spacer in the construct of recombinant AAV vector as an optional element in the design of the AAV vector (the paragraph bridging columns 12 and 13).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the vector taught by of *Dwarki et al*, *Robbins,* and *Pittman et al,* by simply including a DNA spacer in the vector construct as taught by *Gao et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention to optimize and improve the expression capacity of the rAAV vector. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
September 4, 2002

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER